Evaluation and Incorporation of Child/Adult Toxicokinetic Differences in Assessing Risks to Toxicants

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Environmental Issues
Are there differences in toxicokinetics (TK) of xenobiotics between children and adults due to physiological changes and the immaturity of enzyme systems and clearance mechanisms? How can these differences be incorporated into physiologically based pharmacokinetic models that simulate the fate of environmental toxicants in both children and adults? What are the implications of assessing children's risks from environmental agents?

Research
Children's risks from environmental toxicant exposure can be modified by toxicokinetic factors that affect the internal dose of parent chemical and/or active metabolite(s). There are numerous physiologic differences between children and adults that affect TK including size of lipid, tissue compartments, blood flows, protein binding capacity, and immature function of hepatic and extrahepatic organ systems. In collaboration with researchers in Connecticut and at Clark University, Office of Research and Development scientists have been investigating physiologically based toxicokinetic (PBTK) models that can simulate the absorption, distribution, metabolism, and excretion of xenobiotics in both children and adults, allowing for a direct comparison of internal dose and potential risk across species and age groups.

While there are very little PBTK data for environmental agents in children, there is a wealth of such data for therapeutic drugs used in pediatric practice. Using published literature, a children's PK database has been compiled by the ORD-sponsored research that compares PK parameters between children and adults for 45 drugs. This has enabled comparison of child and adult PK function across a number of cytochrome P450 (CYP) pathways, as well as certain Phase II conjugation reactions and renal elimination. These comparisons indicate that premature and full-term neonates tend to have three to nine times longer half-lives than adults for drugs included in the database. This difference disappears at two to six months and beyond this age; half-life can be shorter than adults for specific drugs and pathways. These findings present a TK developmental profile that is relevant to environmental toxicants metabolized and cleared by the pathways represented in the database.

Impact/Outcomes

Research efforts are ongoing and critical in the ORD to enhance understanding of toxicokinetic/toxicodynamic differences across life stages and to better characterize uncertainties in risk assessment of children and other sensitive subgroups within populations. ORD scientists presented these findings and published them in peer-reviewed scientific literature. The U.S. Environmental Protection Agency (U.S. EPA) program offices and external stakeholders are likely to use this approach for defining internal target dose evaluating risk to children.